ACCESSION NUMBER: 136:263158 CA <<LOGINID::20060914>>
TITLE: Benzimidazolyl-substituted quinolinone derivatives and analogs, with inhibitory action against vascular endothelial growth factor receptor tyrosine kinase, and useful as anticancer agents
INVENTOR(S): Renhowe, Paul; Pecchi, Sabina; Machajewski, Tim; Shafer, Cynthia; Taylor, Clarke; McCrea, Bill; McBride, Chris; Jazan, Elisa; Wernette-Hammond, Mary-Ellen; Harris, Alex
PATENT ASSIGNEE(S): Chiron Corporation, USA
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CODEN: PIXXD2
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WO 2002022598	A1	20020321	WO 2001-US42131	20010911
WO 2002022598	C1	20021121		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2421120	AA	20020321	CA 2001-2421120	20010911
AU 2001093275	A5	20020326	AU 2001-93275	20010911
EP 1317442	A1	20030611	EP 2001-973722	20010911
EP 1317442	B1	20051116		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001013757	A	20040302	BR 2001-13757	20010911
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ES 2250480	T3	20060416	ES 2001-1973722	20010911
EP 1650203	A1	20060426	EP 2005-17665	20010911
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
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PRIORITY APPLN. INFO.:			US 2000-232159P P	20000911
			AU 2001-293275 A3	20010911
			EP 2001-973722 A3	20010911
			US 2001-951265 A1	20010911
			WO 2001-US42131 W	20010911
			US 2002-284017 A1	20021030

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OTHER SOURCE(S): MARPAT 136:263158
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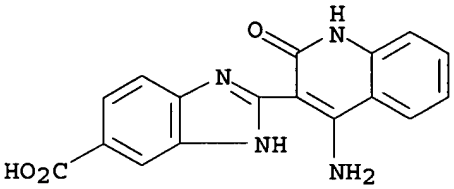
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. of formulas I and II are provided [for I: Z = O, S, (un)substituted NH; Y = certain OH derivs., CHO, esters and amides of CO2H, certain NH2 derivs.; R1-R4 = H, halo, cyano, NO2, OH or derivs., NH2 or derivs., (un)substituted amidinyl, guanidinyl, alk(en/yn)yl, aryl, heterocyclyl, CHO, CO2H and esters and amides; R5-R8 = H, halo, NO2, OH or derivs., NH2 or derivs., SH or derivs., cyano, etc.; R9 = H, OH, (un)substituted alkoxy or aryloxy, NH2 or derivs., (un)substituted alkyl or aryl, CHO, alkanoyl, aroyl; for II: A, B, D, E = C or N, with at least one being N; Y = H, OH or derivs., SH or derivs., NH2 or derivs., cyano, various acyl groups, (un)substituted alk(en/yn)yl, aralkyl, heterocycloalkyl, aryl, etc.; R1-R8 = H, halo, NO2, cyano, OH or derivs., NH2 or derivs., acyl, SH or derivs., etc.; R9 = H, OH, (un)substituted alkoxy, aryloxy, NH2 or derivs., aryl, CHO, alkanoyl, aroyl]. Also provided are pharmaceutical formulations including the compds. or their pharmaceutically acceptable salts and a pharmaceutically acceptable carrier, which may be prepared by mixing the compds. or salts with a carrier and water. A disclosed method of treating a patient includes administering a pharmaceutical formulation according to the invention to a patient. Claims include tautomers of the compds., pharmaceutically acceptable salts, and pharmaceutically acceptable salts of the tautomers. I and II are inhibitors of receptor tyrosine kinases, and particularly of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase. As such, they are inhibitors of angiogenesis, and thereby act as anticancer agents. Approx 270 invention compds. are listed, with detailed prepns. given for about 50 compds. Several general preparatory methods are discussed in detail. For instance, cyclocondensation of Et 2-(benzimidazol-2-yl)acetate with the corresponding ortho-amino nitrile (prepns. given), carried out in refluxing ClCH2CH2Cl in the presence of SnCl4, gave the invention quinolinone III. Many compds. I and II had in vitro IC50 values of less than 10 μM with respect to flt-1 (VEGFR1), KDR (VEGFR2) and bFGF kinases (recombinant, expressed in Sf9 insect cells).

IT 405168-78-7P, 2-(4-Amino-2-oxo-1,2-dihydroquinolin-3-yl)-1H-benzimidazole-6-carboxylic acid
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(drug candidate; preparation of benzimidazolyl-substituted quinolinone derivs. and analogs as VEGFR tyrosine kinase -inhibiting anticancer agents)

RN 405168-78-7 CA

CN 1H-Benzimidazole-5-carboxylic acid, 2-(4-amino-1,2-dihydro-2-oxo-3-quinolinyl)- (9CI) (CA INDEX NAME)


O
H
N
N
NH
HO2C
NH2